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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,623	07/16/2003	Ben-Zion Dolitzky	1662/60707	2588

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KENYON & KENYON LLP  
ONE BROADWAY  
NEW YORK, NY 10004

EXAMINER
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STOCKTON, LAURA LYNNE

ART UNIT	PAPER NUMBER
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1626

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05/19/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/621,623		DOLITZKY ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Laura L. Stockton, Ph.D.		1626	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 January 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 11-30 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 11-30 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                         |                                                                             |
|-----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                                |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____                                                             | 6) <input type="checkbox"/> Other: _____                                    |

Art Unit: 1626

**DETAILED ACTION**

**Claims 11-30 are pending in the application.**

***Election/Restrictions***

Applicant's election without traverse of Group II (claims 11-18) in the reply filed on October 28, 2005 was acknowledged in a previous Office Action. The requirement was deemed proper and therefore made FINAL in a previous Office Action.

Claims 1-10 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the reply filed on October 28, 2005. Claims 1-10 have been cancelled per the Amendment filed January 14, 2008.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-14, 19-21, 22, 25 and 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 11, it is unclear how the combination is maintained at the temperature range. The "heating" should not have been deleted from the claim.

Claim 22 lacks antecedent basis from claim 21.

Art Unit: 1626

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

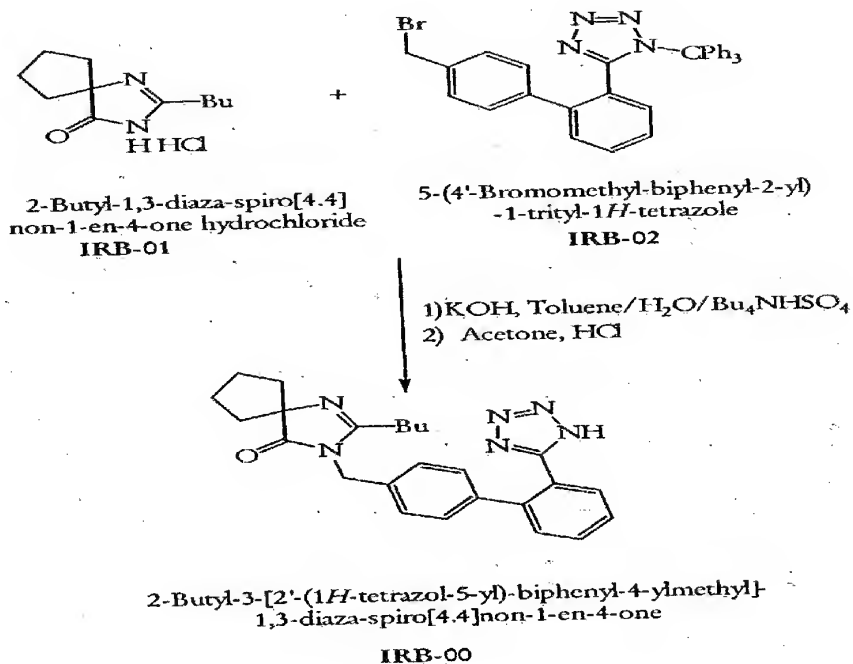
Claims 11-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernhart et al. {U.S. Pat. 5,270,317} in view of Anderson et al. {WO 99/38847}, Cuadro et al. {Synthetic Communications, (1991), 21(4), pages 535-544} and Alvarez-Builla et al. {Tetrahedron (1990), 46(3), pages 967-978}.

***Determination of the scope and content of the prior art (MPEP §2141.01)***

Applicant claims a process of making irbesartan by the process found in instant Figure 1 (reproduced below).

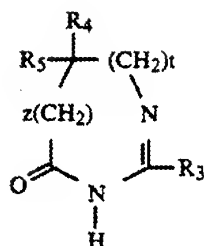
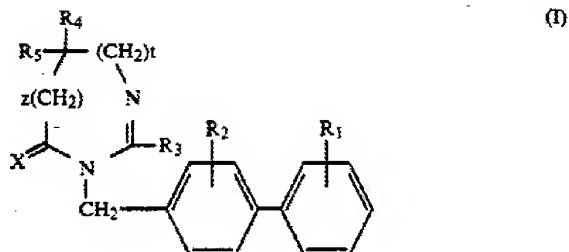
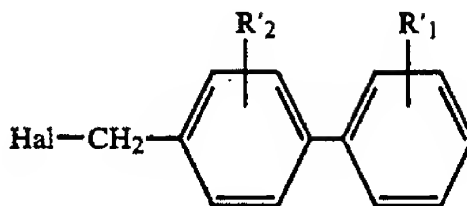
Art Unit: 1626

**Figure 1**  
**PTC Route to Irbesartan**



Bernhart et al. (columns 1-4) teach a process of making N-substituted heterocyclic compounds of formula (I) (reproduced below) wherein a compound of formula 2 (reproduced below) is reacted with a compound of formula 3 (reproduced below).

Art Unit: 1626

**2****3**

Note in Bernhart et al. that variable  $R_2$  can be hydrogen and  $R_1$  can represent tetrazolyl or cyano (column 1, lines 52-56). Also see the process in column 9, lines 54-62, the products and the processes of making Example 5A) and Example 5C) in columns 20 and 21. Bernhart et al. further teach that it is well within the skill of one skilled in the art to convert, for example,

Art Unit: 1626

tetrazolyl protected by a trityl group or a cyano group to a tetrazolyl group by known methods (column 9, lines 15-28).

***Ascertainment of the difference between the prior art and the claims***

***(MPEP §2141.02)***

Bernhart et al. do not teach the use of a phase transfer catalyst in the process. However, Anderson et al., which reference Bernhart et al. on page 2, teach the use of a phase transfer catalyst in the process taught by Bernhart et al. (page 4). Anderson et al. further teach the temperature, pressure, solvents, etc. (pages 7-10). Cuadro et al. teach the N-alkylation of azole compounds in a biphasic system and the use of phase transfer catalysts (page 537). Cuadro et al. reference Alvarez-Builla et al. (see Reference 14 on page 543) for additional phase transfer catalyst (see the last paragraph on page 968 of Alvarez-Builla et al.).



***Finding of prima facie obviousness--rational and motivation (MPEP  
§2142-2413)***

The claimed process is no more than a selective combination of prior art teachings done in a manner obvious to one of ordinary skill in the art since each step of the process appears to be relatively complete in itself and there is no indication of an interaction between steps of such a type that would lead one of ordinary skill in the art to doubt that a substitution of alternative steps known to the art could be made.

*In re Mostovych*, 144 USPQ 38 (1964).

One skilled in the art would thus be motivated to combine the teachings of Bernhart et al., Anderson et al., Cuadro et al. and Alvarez-Builla et al. to arrive at the instant claimed process with the expectation of obtaining Irbesartan in short duration and with increased productivity as taught by Anderson et al. (page 7, lines 27 through to page 8, lines 1-2). The instant claimed process would have been suggested to

Art Unit: 1626

one skilled in the art and therefore, would be obvious to one skilled in the art.

### ***Response to Arguments***

Applicant's arguments filed January 14, 2008 have been fully considered but they are not persuasive. Applicant argues that: (1) Bernhart et al. do not teach the use of a phase transfer catalyst in the process; (2) neither Anderson et al., Cuadro et al. nor Alvarez-Builla et al. teach the process of making 2-butyl-3-[2'-(triphenylmethyl-tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one; (3) in order to arrive at the recitations of claims 11-20 from the disclosure in Bernhart et al., one skilled in the art would have to substitute 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole for 5-(4'-bromomethyl[1,1'-biphenyl]-2-carbonitrile in Step A as well as replace the DMF solvent in Step A with a biphasic system and add a phase transfer catalyst; and (4) using the

Art Unit: 1626

triphenylmethyl tetrazole moiety as instantly claimed is advantageous because the resulting irbesartan intermediate can be converted to irbesartan by the simple step of removing the triphenylmethyl protecting group whereas the amounts of azide and cyano groups must be limited in an irbesartan drug product.

Applicant's arguments have been considered but have not been found persuasive. Applicant argues that Bernhart et al. do not teach the use of a phase transfer catalyst in the process. As stated above, it was acknowledged as a difference in the above rejection that Bernhart et al. do not teach the use of a phase transfer catalyst in the process. However, as also stated above, Anderson et al. reference Bernhart et al. on page 2 and teach the use of a phase transfer catalyst in the process taught by Bernhart et al. (page 4).

Applicant argues that neither Anderson et al., Cuadro et al. nor Alvarez-Builla et al. teach 2-butyl-

Art Unit: 1626

3-[2'-(triphenylmethyl-tetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one. In response, each of Anderson et al., Cuadro et al. and Alvarez-Builla et al. are secondary references and as such, are not expected to have every claim limitation. As stated in the previous Office Action, the test for combining references is not what individual references themselves suggest but rather what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (1971). While a deficiency in a reference may overcome a rejection under 35 U.S.C. § 103, a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. In re Lyons, 150 U.S.P.Q. 741, 746 (C.C.P.A. 1966). One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642

Art Unit: 1626

F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co.,  
800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that in order to arrive at the recitations of claims 11-20 from the disclosure in Bernhart et al., one skilled in the art would have to substitute 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole for 5-(4'-bromomethyl[1,1'-biphenyl]-2-carbonitrile in Step A as well as replace the DMF solvent in Step A with a biphasic system and add a phase transfer catalyst. In response, Bernhart et al. (R<sub>1</sub> can represent tetrazolyl or cyano - column 1, lines 52-56) alone teach the interchangeability of 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole and 5-(4'-bromomethyl[1,1'-biphenyl]-2-carbonitrile. Therefore, it is not understood why Applicant stated there would have to be a substitution. The biphasic system and the phase transfer catalyst are taught by the secondary references.

Art Unit: 1626

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Anderson et al. (page 2) reference Bernhart et al. and Cuadro et al. (Reference 14 on page 543) reference Alvarez-Builla et al. Therefore, there is motivation to combine the teachings of the prior art.

Applicant argues that using the triphenylmethyl tetrazole moiety, as instantly claimed, is advantageous because the resulting irbesartan intermediate can be converted to irbesartan by the simple step of removing the triphenylmethyl protecting group whereas the amounts of azide and cyano groups must be limited in an

Art Unit: 1626

irbesartan drug product. In response, as stated above, Bernhart et al. teach that it is well within the skill of one skilled in the art to convert, for example, tetrazolyl protected by a trityl group (i.e., triphenylmethyl) or a cyano group to a tetrazolyl group by known methods (column 9, lines 15-28). For the reasons given above, the instant claimed invention would have been suggested to one skilled in the art and therefore, the instant claimed invention would have been obvious to one skilled in the art.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: 1626

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura L. Stockton whose telephone number is (571) 272-0710. The examiner can normally be reached on Monday-Friday from 6:15 am to 2:45 pm. If the examiner is out of the Office, the examiner's supervisor, Joseph McKane, can be reached on (571) 272-0699.



Art Unit: 1626

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

The Official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Laura L. Stockton/  
Laura L. Stockton, Ph.D.  
Patent Examiner  
Art Unit 1626, Group 1620  
Technology Center 1600

May 19, 2008